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ORIGINAL ARTICLE

Chyle leakage patterns and management after oncologic esophagectomy: A retrospective cohort study

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Abstract

Background: This study aims to evaluate the incidence and characteristics of chyle leakage after curative oncologic esophagectomy, and the effectiveness of thoracic duct ligation.

Methods: This is a retrospective cohort study using the medical records of 1514 patients who underwent curative esophagectomy for esophageal cancer between September 1994 and December 2010. Patients whose pleural fluid analysis corresponded to chyle were included, and drainage patterns by different management groups were examined with multilevel models. The chyle leakage patterns during the time before and after duct ligation were also evaluated, adjusting for demographics, clinical characteristics, and treatment.

Results: The prevalence of chyle leakage after esophagectomy was 3.8%. The three management groups were as follows: (i) conservative–controlled only with conservative management; (ii) surgical I–duct ligation during the esophagectomy; and (iii) surgical II–duct ligation after the esophagectomy. Pattern analysis determined that drainage of the conservative group was ~400 mL/day (maximum on postoperative days [POD] = 9.2); drainage of surgical II was ~1000 mL/day (maximum on POD = 18.1). On average, thoracic duct ligation was performed 18.7 days after the esophagectomy, and drainage significantly decreased after duct ligation (*P*-value <0.001).

Conclusions: There was a clear pattern of lower chyle leakage with the patients requiring conservative management compared with those requiring surgical management. Active and prompt surgical management needs to be considered in the early postoperative phase for patients with high-output (over 1000 mL/day) chyle leakage after esophagectomy.

Introduction

Chyle leakage – one of the most challenging complications following an esophagectomy – can lead to hypovolemia, metabolic and nutritional depletion, infection, and even death.[1–3] The leakage occurs in 1.1 to 3.7% of esophagectomy patients; mortality occurs in excess of 50% of patients.[4–7] Although the mortality rate has decreased as a result of active management, there is still no consensus or specific clinical guidelines for the effective management of chyle leakage.[2,3,8]

Conservative management (no enteral feeding with total parenteral nutrition) of chyle leakage is usually chosen to start with, and surgical management (thoracic duct ligation) is performed when conservative management is not effective.[2,8,9] Cerfolio *et al.* reported the effectiveness of aggressive treatment of chylothorax,[10] and some studies have also claimed that aggressive management (thoracic duct ligation) had better outcomes than conservative management.[11–13] However, other studies have reported different results, preferring alternative, minimally invasive management

methods.[1,14–16] Furthermore, little is known in terms of detailed management methods and outcomes of chyle leakage after oncologic esophagectomy, such as drainage patterns of chyle and the effectiveness of duct ligation. This study evaluates the incidence and clinical characteristics of chyle leakage after curative oncologic esophagectomy and the effectiveness of thoracic duct ligation for chyle leakage.

Materials and methods

Study design and population

This is a retrospective cohort study using medical records of 1514 patients following curative esophagectomy for esophageal cancer between September 1994 and December 2010 at a university-based, tertiary hospital in Seoul, Korea. Patient eligibility criteria included the following: (i) patients who had curative resection for esophageal cancer; (ii) whose triglyceride level was over 110 mg/dL; or (iii) whose triglyceride level was between 50 to 110 mg/dL, but with lipoprotein analysis were found to have chylomicrons.

Triglyceride levels were measured by pleural fluid and ascites tests in patients suspected of having chyle leakage because of the nature or high amount of drainage. Chyle leakage was suspected if the drainage was milky, a cloudy color, or the amount of drainage rapidly increased after feeding. Of the total 1514 patients, 323 patients (21.3%) were tested for triglyceride levels in pleural fluid; 57 patients who had chyle leakage were included in the study. In light of their clinical relevance, the chyle leakage patterns were assessed for 60 postoperative days (POD). This study was reviewed and approved by the institutional review board (IRB) of the Sungkyunkwan University School of Medicine's Samsung Medical Center.

Surgery

An intrathoracic esophagectomy was performed via right thoracotomy, intrathoracic anastomosis, and two-field lymph (thorax and abdomen) node dissection, or by a so-called Ivor Lewis operation, as conducted for middle and lower-third esophageal cancer. The conduit was usually through the stomach without prominent gastric problems. When pulmonary complications or periesophageal adhesions were anticipated, transhiatal esophagectomy (TH) was sometimes used to avoid thoracic incision and pulmonary complications. Cervical anastomosis on the left side of the neck and abdominal lymph node dissection was used in those cases. Upper-third esophageal cancer was treated with three-field lymph node dissection (abdomen, thorax, and neck), intrathoracic esophagectomy, and cervical anastomosis on the left side of the neck. Two-field lymph node dissection was defined as resection of lymph nodes within the mediastinal and abdominal lymph node stations. The paraesophageal nodes, bilateral intrathoracic recurrent laryngeal nerve chain nodes, subaortic arch nodes, and subcarinal nodes were dissected through a right thoracotomy. Bilateral recurrent laryngeal nerves were carefully exposed, and the lymph nodes along these nerves were completely removed. The paracardiac nodes, celiac nodes, nodes along the left gastric artery, and common hepatic artery nodes were dissected through an upper midline laparotomy. Three-field lymph node dissection was defined as the resection of lymph nodes within the cervical lymph node station in addition to the two above-mentioned lymph node stations. The cervical recurrent laryngeal nerve chain nodes and internal jugular nodes below the level of the cricoid cartilage, supraclavicular nodes, deep cervical nodes, and cervical paraesophageal nodes were dissected bilaterally through a cervical collar incision.

Management of chyle leakage

All patients in our study who had chyle leakage primarily received conservative management, except patients who had duct ligation during surgery. Conservative management consisted of no enteral feeding and total parenteral nutrition. If chyle leakage was not controlled and continued to increase with conservative management, other interventions were attempted, including pleurodesis and Octreotide (Sandostatin, Novartis), a long-acting somatostatin analog. If the drainage continued and exceeded more than 1000 mL/day, even after these non-surgical managements, surgical intervention (ligation of the thoracic duct) was implemented.

If the drainage decreased to less than 100 mL/day and if no radiographic evidence of chylous effusion was seen, oral feeding was attempted, starting with water, a no fat diet, and, ultimately, a normal diet. The drain was then removed and patients were discharged if they had no other complications.

For clinical characteristics, age, histology, site of tumor, preoperative nutritional status, tumor (T) and node (N) stage, history of neoadjuvant or adjuvant treatment were collected. Site of the tumor: cervical esophageal cancer was considered as upper esophagus; an esophagogastric junction tumor was considered as lower esophagus. T and N stage were determined according to the American Joint Committee on Cancer Cancer Staging Manual, 7th edition.[17] Operative information: kinds of esophagectomy, field(s) of lymph node dissection, methods of anastomosis, and conduit and performance of feeding jejunostomy were collected. Four kinds of major complications were assessed: (i) 30-day mortality: mortality happened within 30 days after esophagectomy; (ii) lung complications: any pulmonary complications including acute lung injury, acute respiratory distress syndrome, or pneumonia, which required a mechanical ventilator for more than seven days; (iii) hoarseness: steady voice change because of injury to the recurrent laryngeal nerve; and (iv) wound:

any wound problems such as infection or dehiscence requiring additional management beyond routine dressing. The length of hospital stay ranged from surgery to discharge. No residual chyle leakage was defined as a patient who had no radiological evidence of chylous effusion or problems related to chyle leakage after removal of the drainage tube.

Statistical analysis

Descriptive statistics were used to summarize patient characteristics and outcomes; differences in baseline clinical characteristics, operative information, and surgical outcomes were compared by management group using χ^2 tests. Fisher's exact test was used when the number of data was below five for categorical variables and *t*-tests were used for continuous variables. T-tests and Mann–Whitney–Wilcoxon tests were used depending on outcome distribution.

Multilevel models were used to assess the change of chyle leakage (amount of drainage) over time and case-wise deletion was used for the missing data. A linear spline knot was made at the time the person had duct ligation, dividing the time variable into two parts: time before duct ligation and time after duct ligation. Potential confounders include baseline demographics, clinical characteristics, and treatments, as shown in Table 1. Adjusted means and the 95% confidence intervals were estimated from linear prediction following mixed-effect regression of chyle leakage patterns on the time before duct ligation and the time after duct ligation, adjusting for potential confounding variables. All analyses were conducted using Stata 12.0. *P*-values <0.05 were considered statistically significant.

Results

Characteristics of the study population

Chyle leakage occurred in 57 (3.8%) patients out of the total 1514 patients; all patients were male and had squamous cell carcinoma (Table 1). About half of the chyle leakage developed in mid-thoracic esophageal cancer. The preoperative nutritional status of the study population was good: mean body mass index (BMI) was 20.9, and serum protein and albumin levels were within normal limits. Pathologic T3 or N1 was common; 21% and 29.8% of the patients received neoadjuvant and adjuvant treatment, respectively. Over 94% of the esophagectomy was performed transthoracically, and more than 70% of the lymph node dissections were performed in the abdomen and thorax together (Table 1). Intrathoracic anastomosis and a stomach conduit were common in this population.

Among the 57 patients who had chyle leakage, 43 patients (75%) had conservative management, and 14 (25%) received surgical management (thoracic duct ligation) after the conservative management (Table 1). Three of the 14 patients had duct ligation during esophagectomy because the chyle leakage was found during surgery; the last 11 of them had duct ligation after esophagectomy. In this study, we defined three different chyle leakage management groups: (i) conservative group–patients whose chyle leakage was controlled only with conservative management; (ii) surgical group I–patients who had duct ligation during the esophagectomy; and (iii) surgical group II–patients who had duct ligation *after* the esophagectomy.

The conservative group had demographic and clinical characteristics similar to patients who had to receive surgical management, except for the BMI (Table 1). The surgical groups had statistically significantly higher BMI (mean: 22.3, standard deviation [SD]: 3.1) than the conservative group (mean: 20.4, SD: 2.5). They were also more likely to have cervical anastomosis, neck node dissection, and feeding jejunostomy than the conservative group, but it was not statistically significant (Table 1).

Surgical outcomes

The surgical outcomes of patients who had chyle leakage are presented in Table 2. The surgical groups were more likely to have pleurodesis on the ward, but it was not significantly different from the conservative group. Although patients who had duct ligation seemed to have more lung and wound complications than patients whose chyle was successfully managed only by the conservative method, the difference was not statistically significant. The 30-day mortality developed in one (1.7%) patient, but it was a result of acute respiratory distress syndrome. The surgical groups had a much longer length of hospital stay (mean: 60.6, standard error [SE]: 35.4) than the conservative group ($P < 0.01$), but status on discharge was not different between the two groups (Table 2).

Patterns of chyle leakage and management

The patterns of chyle leakage by different groups are shown in Figure 1. The patterns of drainage were more stable in the conservative group than in surgical group I and II (Fig 1). The conservative group reported a maximum amount of drainage for an average of 9.2 days after the esophagectomy; surgical group II had maximum drainage for an average of 18.1 days postoperatively.

The median chyle leakage in the conservative and surgical management groups was 260 and 1020 mL/day, respectively ($P < 0.01$) Similar differences were maintained throughout the study period (all *P*-values <0.01) (Table 3 & Fig 1).

On average, patients received thoracic duct ligation for chyle leakage 18.7 days after esophagectomy; the mean drainage before the thoracic duct ligation was 1360.02 mL and

Table 1 Clinical characteristics and surgical information of the study participants (*N* = 57)

Clinical characteristics	Total *N* = 57	Conservative management† *n* = 43	Surgical management‡ *n* = 14	*P*-value
Age	62.7 ± 8.8	62.3 ± 8.4	63.7 ± 9.6	0.60
Histology				
Squamous cell carcinoma	57 (100)	43 (100)	14 (100)	
Site of tumor				0.79
Upper esophagus	13 (22.7)	9 (20.9)	4 (28.6)	
Mid thorax	28 (49.1)	21 (48.8)	7 (50.0)	
Lower esophagus	16 (28.0)	13 (30.2)	3 (21.4)	
Preoperative nutritional status				
BMI	20.9 ± 2.8	20.4 ± 2.5	22.3 ± 3.1	0.03
Protein	6.8 ± 0.5	6.7 ± 0.5	6.8 ± 0.6	0.84
Albumin	3.9 ± 0.4	3.9 ± 0.4	3.9 ± 0.3	0.96
Pathologic T stage				0.66
In situ	5 (8.7)	3 (7.0)	2 (14.3)	
T1	9 (15.7)	6 (14.0)	3 (21.4)	
T2	9 (15.7)	6 (14.0)	3 (21.4)	
T3	31 (54.3)	26 (60.5)	5 (35.7)	
T4	3 (5.2)	2 (4.7)	1 (7.1)	
Pathologic N stage				0.73
N0	19 (33.3)	13 (30.2)	6 (42.9)	
N1	36 (63.1)	28 (65.1)	8 (57.1)	
N2/N3	1 (1.7)/1 (1.7)	1 (2.3)/1 (2.3)	0 (0)/0 (0)	
Neoadjuvant treatment				0.99
Performed	12 (21.0)	9 (20.9)	3 (21.4)	
Adjuvant treatment				0.19
Performed	17 (29.8)	15 (34.9)	2 (14.3)	
Operative information				
Esophagectomy				0.99
Transthoracic	54 (94.7)	41 (95.3)	13 (92.9)	
Transhiatal	3 (5.2)	2 (4.7)	1 (7.1)	
Lymph node dissection				0.33
None	1 (1.7)	0 (0)	1 (7.1)	
Abdomen	3 (5.2)	2 (4.7)	1 (7.1)	
Abdomen and thorax	39 (68.4)	31 (72.1)	8 (57.1)	
Abdomen, thorax and neck	14 (24.5)	10 (23.3)	4 (28.6)	
Anastomosis				0.75
Cervical	21 (36.8)	15 (34.9)	6 (42.9)	
Intrathoracic	36 (63.1)	28 (65.1)	8 (57.1)	
Conduit				0.99
Stomach	53 (92.9)	40 (93.0)	13 (92.9)	
Colon	4 (7.0)	3 (7.0)	1 (7.1)	
Feeding jejunostomy				0.99
Performed	35 (61.4)	26 (60.5)	9 (64.3)	

†Patients who received no enteral feeding and total parenteral nutrition. ‡Patients who had duct ligation after the trial of conservative management. The data was illustrated with mean ± standard deviation or number (proportion). Continuous variables were expressed as mean with standard deviation. BMI, body mass index; N, node; T, tumor.

after the ligation, 563.00 mL (data not shown). The drainage significantly decreased with surgical management (*P*-value <0.001) (Fig 2).

Discussion

We found that the pattern of chyle leakage was significantly different between patients whose chyle was handled by conservative management only versus patients who ended up having surgical management. Patients who ended up having duct ligation reported on average more than 1000 mL/day drainage – double the amount of drainage in patients who had conservative management. Clearly, the surgical management was effective on excessive chyle leakage, and there was a dramatic decrease of drainage after the duct ligation.

Table 2 Surgical outcomes of conservative and surgical management groups

	Conservative management ($n = 43$) *N* (%)	Surgical management ($n = 14$) *N* (%)	*P*-value
Non-surgical management			
NPO with TPN	35 (81.3)	13 (92.8)	0.42
Octreotide	5 (11.6)	1 (7.1)	1.00
Pleurodesis in ward	5 (11.6)	3 (21.4)	0.39
Complications			
30-day mortality	0 (0)	1 (7.1)	0.24
Lung†	4 (9.3)	4 (28.5)	0.09
Hoarseness	1 (2.3)	0 (0)	0.99
Wound‡	6 (13.9)	3 (21.4)	0.67
Length of hospital stay (days, mean, SE)	36.6, 22.4	60.6, 35.4	<0.01
Status on discharge			0.24
No residual chyle leakage	43 (100)	13 (92.8)	

†Lung, pulmonary complications including acute lung injury, acute respiratory distress syndrome, or pneumonia. ‡Wound, wound problem including infection or dehiscence. NPO, nothing per oral or no enteral feeding; SE: standard error; TPN,, total parenteral nutrition.

Investigators in previous studies proposed that the amount of chyle leakage would be a key factor affecting the decisions regarding aggressive surgical intervention;[10,18,19] however, the studies suggested different cut-off values, and there were no specific guidelines.[4,8,20–22] Previous studies also had a limited time to observe the pattern of chyle leakage in the long term as they were conducted within a relatively short period.[8,10,20] We analyzed the patterns of chyle leakage until postoperative day 60, and those of different management groups were compared. While the patients whose chyle leakage was successfully controlled by conservative management reported an average drainage below 400 mL/day, the surgical group reported more than 1000 mL/day on average, and the drainage kept increasing until duct ligation intervention. Therefore, we suggest that daily drainage (output) over 1000 mL would be an indication for thoracic duct ligation for patients with chyle leakage.

The effectiveness of surgical intervention was clear in our study, and it did not vary according to the time period: the effectiveness of intervention was the same regardless of timing. In our study, however, patients had duct ligation on average 18.7 days after esophagectomy, resulting in a much longer length of hospital stay of the surgical group compared to the conservative group. Although it is a heavy burden for surgeons to have to perform another thoracotomy, the decision needs to be made as soon as possible considering health-

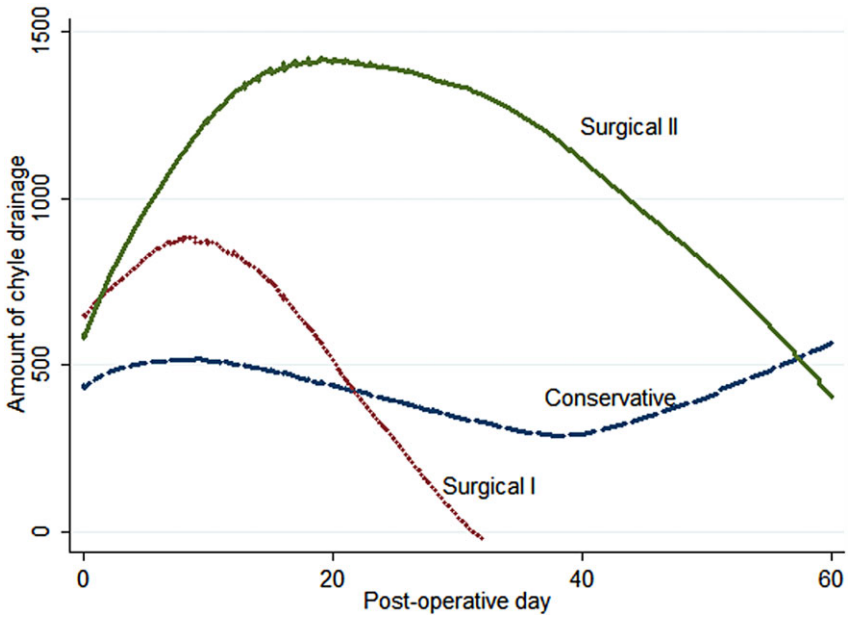

Figure 1 Patterns of chyle leakage by management group. *Conservative – patients whose chyle leakage was controlled only with conservative management; surgical I – patients who had duct ligation during the esophagectomy; and surgical II – patients who had duct ligation after the esophagectomy.

Table 3 Chyle leakage after surgery by management group

Management groups†	Overall	0–6th POD	7–13th POD	14–20th POD	21th-60th POD
Conservative ($n = 43$)	Number of patients				
	43	43	43	32	31
	Drainage (mL/day), median (IQR)				
	260 (90–540)	350 (200–600)	330 (139.5–705)	310 (140–630)	150 (30–340)
Surgical II ($n = 11$)	Number of patients				
	11	11	10	10	8
	Drainage (mL/day), median (IQR)				
	1020 (330–1809)	835 (300–1320)	1311.5(718–2020)	1472.5(718–3080)	920 (270–1790)
P-value	<0.01	<0.01	<0.01	<0.01	<0.01

†Conservative – patients whose chyle leakage was controlled only with conservative management; surgical I – patients who had duct ligation during the operation; and surgical II – patients who had duct ligation after the esophagectomy. IQR, interquartile range; POD, postoperative day(s).

care resource utilization and the patient's quality of life. The results of our study suggest that an early surgical intervention would be effective for patients who have excessive chyle leakage (more than 1000 mL/day). Also, the advanced technique of video-assisted thoracic surgery or the percutaneous technique would help surgeons redo the thoracotomy.[1,15,16]

While all characteristics of the conservative and surgical groups were similar, the surgical group had higher BMIs than the conservative group. In previous studies, although it was not directly related to chyle leakage, there were several reports about the relationship between high BMI and negative postoperative outcomes.[23,24] It is difficult to explain its biologic mechanism; a higher BMI might be a risk factor for excessive chyle leakage requiring surgical management. Therefore, it might be necessary to observe patients with higher BMIs more closely when they have chyle leakage.

This study has several limitations. First, it was based on data from a single institution, the number of patients with chyle leakage was small, and generalizability of the study is limited. However, chyle leakage is a rare complication, and this study covers a relatively large group of patients with oncologic esophagectomy for more than 15 years. Second, there may be missing cases of chyle leakage because of the retrospective cohort study design. We collected information about chyle leakage based on electronic medical records (EMR); therefore, we might have missed cases that were not included in EMR or cases managed without triglyceride tests. The incidence of chyle leakage in our study, however, is similar to previous studies, and we believe that the quality of our study sample is satisfactory. Third, the protocol of conservative management varied in cases, so it would be a confounding factor for analyzing the characteristics of surgical candidates.

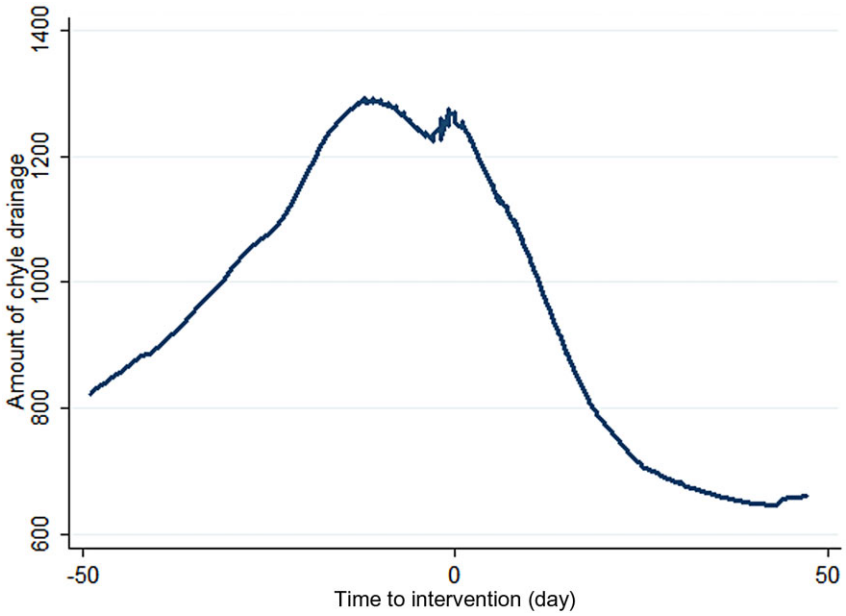

Figure 2 Change of chyle drainage before and after duct ligation.

Despite the limitations, this study provides unique opportunities to evaluate the patterns of chyle leakage and the effectiveness of each management method, controlling for the most important confounder – technical variance among surgeons. In this study, two surgeons who had used similar surgical techniques and performed similar cases of esophagectomy performed all surgeries. In fact, there were no differences in the incidence of chyle leakage and surgical outcomes among patients of the two surgeons (data not shown).

Conclusion

In conclusion, there was a clear pattern of lower chyle leakage with patients requiring conservative management compared to those requiring surgical management. Active, surgical management is necessary in the early postoperative phase for patients with high-output (over 1000 mL per day) chyle leakage.

Disclosure

No authors report any conflict of interest.

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